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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/841,744	04/24/2001	Jorge F. DiMartino	12636-891	5759

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 11/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/841,744	DIMARTINO, JORGE F.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,8-14 and 16-38* is/are pending in the application.

4a) Of the above claim(s) *3,5,29 and 31-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,8-14,16-28 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☒ Interview Summary (PTO-413) Paper No(s). *8/26/03*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

1. Claims 1, 3-5, 8-14 and 16-38 are pending.

Applicants' amendment filed on August 26, 2003 is acknowledged, and applicants' response has been fully considered. Claims 1 and 28 have been amended, and claims 6 and 7 have been cancelled. Claims 3, 5, 29 and 31-38 are non-elected inventions and are withdrawn from consideration. Thus, claims 1, 4, 8-14, 16-28 and 30 are examined.

Rejection Withdrawn

Claim Rejections-Obviousness Type Double Patenting

2. The previous rejection of claims 1, 4, 6-14, 16-18, 28 and 30 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over copending Application No. 09/790,483 (now U. S. Patent 6,613,753) in view of Zhu et al. (Cancer Research 61, 1327-1333) and Saito et al. (Proc. Natl. Acad. Sci. U.S.A. 96, 4592-4597 (1999)), is withdrawn in view of the terminal disclaimer filed by applicants on August 26, 2003.

Claim Objections

3. Claim 28 remains objected to because the claim has not shown the phrase "anti-neoplastic agent selected from the group consisting of" being deleted.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 4, 8-14, 16-28 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a specific cancer such as breast, lung, stomach or thyroid cancer comprising administering decitabine as a DNA methylation inhibitor in combination with a specific histone deacetylase (HDA) inhibitor such as depsipeptide, phenylbutyrate or arginine butyrate, optionally with an antibiotic agent as an anti-neoplastic agent, does not reasonably provide enablement for a method of treating all cancers with a combination therapy comprising administering decitabine or 5-azacytidine in combination with a histone deacetylase inhibitor, optionally with an antibiotic agent, wherein the cancer, the HDA inhibitor and the antibiotic agent are not defined. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1, 4, 8-14, 16-28 and 30 encompass a method of treating cancer with a combination therapy comprising administering decitabine or 5-azacytidine in combination with a histone deacetylase inhibitor (claims 1, 4, 8-14, 16-27), optionally with an antibiotic agent (claims 28 and 30). The specification, however, only discloses cursory conclusions without data supporting the findings, which state that the invention provides a method of treating a disease such as cancer using a combination therapy including a DNA methylation inhibitor and a histone deacetylase inhibitor, which triggers cancer cell death through reestablishment of intrinsic death mechanism of cells such as growth arrest, differentiation and apoptosis through activation of genes selectively silenced in cancer cells, and the cancer cells sensitized by such a combination die quickly or become more prone to cell death signals sent by administration of conventional anti-neoplastic agents (page 8, lines 8-18). There are no indicia that the present application

enables the full scope in view of a method of treating various cancers using the combination therapy of decitabine or 5-azacytidine and a histone deacetylase inhibitor as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the absence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding various cancers and histone deacetylase inhibitors, which are not adequately described or demonstrated in the specification.

(2). The absence of working examples:

There are no working examples indicating the claimed methods in association with the variants. The specification has not demonstrated the effect of the combination therapy in the treatment of various cancers.

(3). The state of the prior art and relative skill of those in the art:

The prior art (e.g., Zhu *et al.*, Cancer Research 61, 1327-1333 (2001)) indicates histone deacetylase (HDA) inhibitors such as depsipeptide (FR901228) and trichostatin A induce apoptotic cell death, and this induced apoptosis is greatly enhanced in the presence of the DNA methyltransferase inhibitor, 5-aza-2'-deoxycytidine (decitabine). However, the general

knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific teachings on treating conditions for treating various cancers using decitabine or 5-azacytidine with a specific histone deacetylase inhibitor and the effect of the combination therapy to be considered enabling for variants.

(4). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method of treating cancer with a combination therapy comprising administering decitabine or 5-azacytidine in combination with a histone deacetylase inhibitor, optionally with an antibiotic agent. The specification indicates methylation of DNA or deacetylase of histone plays an important role in regulation of gene expression, and the disease such as cancer is related to aberrant silencing of gene expression, thus, a combination therapy of a DNA methylation inhibitor such as decitabine and 5-azacytidine, and a histone deacetylase inhibitor can be used to treat cancer through reestablishment of gene transcription (pages 1, 15-18, 20-21); and further asserts that various cytidine analogs or derivatives can be used as a DNA methylation inhibitor and various histone deacetylase inhibitors such as hydroxymic acids, cyclic peptides, benzamides, butyrates and depudecin can be used as a histone deacetylase inhibitor (pages 8-9). However, the specification has not demonstrated the effect of the combination therapy although the doses of decitabine, depsipeptide, phenylbutyrate and arginine butyrate have been indicated (pages 11 and 37). Moreover, the specification has not shown the treating conditions such as the dosage, the time, and the frequency of the treatment using decitabine with various histone deacetylase inhibitors other than depsipeptide, phenylbutyrate and arginine butyrate in the treatment of various cancers. There are no working examples indicating the effect

of combination therapy in the claimed method. Since the specification fails to provide sufficient teachings on the treatment of various cancers and the effect of using combination therapy, it is necessary to have additional guidance and to carry out further experimentation to assess the effect of the combination therapy using decitabine or 5-azacytidine with various histone deacetylase inhibitors in the treatment of cancer.

(5). Predictability or unpredictability of the art:

The claims encompass a method of treating cancer with a combination therapy comprising administering a DNA methylation inhibitor such as decitabine or 5-azacytidine and a histone deacetylase inhibitor, optionally with an antibiotic agent. However, the use of specific inhibitors in the combination therapy, the treating conditions for treating various cancers and the effects of inhibitors in the treatment are not adequately described in the specification, the invention is highly unpredictable regarding the outcome of the treatment.

(6). Nature of the Invention

The scope of the claims encompasses using combination therapy in the treatment of various cancers, but the specification does not demonstrate the effect of combination therapy using decitabine or 5-azacytidine with various histone deacetylase inhibitors. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broader than the enabling disclosure. The working examples do not demonstrate the outcome of the treatment, which is unpredictable, and the guidance and the teaching in the specification is limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effect of the treatment using decitabine or 5-azacytidine with various histone deacetylase inhibitors.

In response, applicants indicate Examiner has not satisfied the requirement of establishing a reasonable basis to question the enablement for all other cancers than breast, lung, stomach and thyroid cancers (page 8 of the response). The response has been considered, however, the argument is not found persuasive because the claim (e.g., claim 1) recites the treatment of cancer, which includes any cancer, using decitabine or 5-azacytidine in combination with a histone deacetylase inhibitor, it does not identify a specific cancer to be treated and a specific HAD inhibitor to be used in the combination therapy, nor indicates the effects of decitabine or 5-azacytidine in combination with a histone deacetylase inhibitor in the treatment, thus the full scope of the claim is not enabled by the disclosure for the reasons as indicated in the sections above (see the pages 4-6).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1, 4, 8-14, 16-28 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4, 8-14, 16-28 and 30 are indefinite because the claim lacks an essential step in the method of treating cancer with a combination therapy. The omitted step is the outcome of the treatment. Claims 4, 8-14, 16-28 and 30 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

In response, applicant indicates in determining whether an unclaimed feature is essential or critical, the entire disclosure must be considered and features which are merely preferred are

not to be considered critical, and "the outcome of the treatment" is not disclosed because the outcome is not critical; the treatment outcome, according to the present invention, can include cancer growth arrest, attenuation in cancer growth, or complete cure of cancer; as there is no particular feature of the outcome of treatment critical to the claimed invention, it is not necessary to claim such limitation (page 9 of the response). The argument is not found persuasive because without recitation of the outcome of the claimed method, it is not clear whether the treatment would be effective, which is related to the requirement of definiteness of 112, second paragraph, and the treatment outcome indicated in the response is not cited in the claim, thus, the effectiveness of the treatment is uncertain.

Conclusion

6. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

November 18, 2003

CHRISTOPHER S. F. LOW
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